

Vol 5, No 8

Best Available Copy

August 1987

EXHIBIT 1

CLINICAL ONCOLOGY

Official Journal of the American
Society of Clinical Oncology

GRUNE & STRATTON
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Phase I Trial of Taxol Given as a 24-Hour Infusion Every 21 Days: Responses Observed in Metastatic Melanoma

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Taxol, a plant product, has significant activity against certain rodent and human xenograft tumors. It promotes microtubule assembly in vitro, in contrast to vinca alkaloids, which inhibit assembly. In this phase I study, taxol was administered as a 24-hour continuous intravenous (IV) infusion in 65 courses to 26 patients. A premedication regimen of dexamethasone, cimetidine, and diphenhydramine was used to prevent the acute hypersensitivity reactions observed in previous studies of taxol. Only one episode of mild stridor occurred in this study. Peripheral neuropathy was the dose-limiting toxicity and was observed in 40% of patients treated at a dose of 250 mg/m². Significant neutropenia of brief duration was also

common. Pharmacokinetic studies by a high-performance liquid chromatography (HPLC) method demonstrated that drug plasma concentrations increased during the 24-hour infusion and then declined rapidly. Peak plasma concentrations correlated with dose, and < 5% of taxol was excreted in the urine. Most of the drug was bound to serum components. Partial responses of more than 3 months' duration were observed in four of 12 melanoma patients treated. The recommended phase II dose of taxol on this schedule is 250 mg/m². Priority should be given to the study of taxol in melanoma.

J Clin Oncol 5:1232-1239. © 1987 by American Society of Clinical Oncology.

TAXOL is a novel plant product isolated from the stem bark of the western yew, *Taxus brevifolia*,¹ and is the prototype of a new class of antitumor drugs with a unique mechanism of action. Taxol promotes microtubule assembly in vitro,² in contrast to vinca alkaloids, which inhibit assembly. Microtubules polymerized in the presence of taxol are resistant to depolymerization by cold (4°C), or calcium (4 mmol/L), conditions known to depolymerize microtubules. Cell culture experiments have demonstrated that the drug stabilizes cytoplasmic microtubules and modifies their display.³ The drug blocks cell replication in the G₂ and M phases of the cell cycle and inhibits fibroblast cell migration. This probably results from the direct action of taxol on microtubules, since drug-treated cells are unable to depolymerize their microtubule cytoskeletons. This may account for the observed antitumor activity of the drug. The binding of (³H) taxol to

microtubules in vitro and in cells has been demonstrated,^{4,6} and the molecular pharmacology of taxol was recently reviewed.^{7,8}

Preclinical studies have demonstrated that taxol has significant antitumor activity against B16 melanoma, human MX-1 mammary tumor xenograft, L1210 and P388 leukemias, and the CX-1 colon and LX-1 lung tumor xenografts.⁹ In animal studies, the main toxic effects of taxol were most evident in organs with high cell turnover: bone marrow, gastrointestinal tract, and testes (male rodents only). The vehicle itself (cremophor EL) produced hypotension in dogs.

Phase I trials of taxol have been conducted in the United States at six institutions,¹⁰⁻¹⁵ using various infusion schedules. A 24-hour continuous intravenous (IV) infusion schedule was adopted in this study to establish dose-limiting toxicity and determine if previous toxicities could be modified. The starting dose of 150 mg/m² was based on data from a previous phase I study on this schedule at another institution.¹⁴

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Submitted November 3, 1986; accepted March 11, 1987.

Supported in part by Grant No. 2P30CA13330-15 awarded by the National Cancer Institute, DHHS.

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0732-183X/87/0508-0007\$3.00/0

PATIENTS AND METHODS

Patient Selection

All patients had histologically documented advanced solid tumors and had failed conventional chemotherapy or had a tumor for which no conventional therapy exists. All patients had recovered from the toxicities of prior chemotherapy or radiother-

apy and had adequate bone marrow function (WBC > 4,000 cells/ μ L and platelets > 100,000/ μ L), adequate liver function (bilirubin < 1.5 mg/100 mL), and adequate renal function (creatinine < 1.5 mg/100 mL). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Patients were informed of the phase I investigational nature of the treatment and the toxicities that might be reasonably anticipated from such treatment. The study was approved by the Albert Einstein College of Medicine and Montefiore Medical Center Institutional Review Boards, and written informed consent was obtained from each patient.

Study Parameters

Prior to therapy, all patients had a complete history and physical examination, complete blood count and platelet count, serum biochemical and electrolytes profile, urinalysis, chest x-ray, and ECG. Interval studies were repeated 7, 14, and 21 days after the infusion. Assessments of antitumor response were made every 21 days. A partial response was defined as at least a 50% decrease in the product of the longest perpendicular diameters of all measurable lesions without symptomatic deterioration or the appearance of new lesions. A minimal response was defined as less objective decrease in measurable tumor without other evidence of progression.

Drug Information, Formulation, and Treatment Schedule

Taxol was supplied by the National Cancer Institute (NCI; Bethesda, MD) as a concentrated sterile solution, 6 mg/mL in a 5-mL ampule (30 mg/ampule) in polyoxyethylated castor oil (cremophor EL) 50% and dehydrated alcohol USP, 50%. For each patient, one-third the appropriate dose of taxol was further diluted in 500 mL of 5% dextrose in water prior to administration, and solutions were prepared every eight hours during the 24-hour infusion.

A small number of fibers (within acceptable levels of USP particulate matter test for large volume parentals) have occasionally been observed in the preparation. Therefore, in-line filtration with a 0.2- μ m filter was used with all taxol infusions.

Taxol was administered as an IV infusion over 24 hours. Courses were repeated every 3 weeks. Due to known toxicity of taxol and/or of the cremophor vehicle, the following precautions prior to treatment for the possibility of acute hypersensitivity reaction were taken (see Table 1): (1) 14 hours and seven hours before taxol administration, patients received dexamethasone, 20 mg orally. (2) One hour before taxol administration, patients received parenteral diphenhydramine, 25 mg and cimetidine, 300 mg. (3) Parenteral epinephrine and diphenhydramine were immediately available during the infusion. (4) Patients were monitored continually for at least the first 30 minutes of the infusion by a physician or research nurse so that immediate intervention would occur in response to signs or symptoms of an untoward reaction.

Pharmacokinetic Methods

At specified intervals during and after taxol administration, heparinized blood samples were obtained and plasma was prepared by centrifugation. Initial studies indicated that taxol was stable in plasma stored at -20°C . To prepare samples for high-

Table 1. Treatment Schedule

Premedication	Dose	Route	Time
Dexamethasone	20 mg	Oral	7 and 14 h pre-taxol
Diphenhydramine	25 mg	IV	1 h pre-taxol
Cimetidine	300 mg	IV	1 h pre-taxol

performance liquid chromatography (HPLC) analysis, 0.6 mL of plasma was combined with 1 mL of ice-cold acetonitrile. After one hour, the samples were centrifuged in a microcentrifuge (20 minutes at 5°C). The supernatant was evaporated to dryness under reduced pressure, and the sample was resuspended in 40 μ L methanol immediately before HPLC analysis. Urine samples, collected during the 24-hour infusion and for 24 hours postinfusion, were analyzed directly.

Extracted samples (20 μ L) were analyzed by HPLC, as previously described,¹⁶ using a Whatman (Clifton, NJ) Partisil 10 ODS-3 column (4.6 \times 250 mm) at 40°C on a Hewlett Packard (Palo Alto, CA) HP1090 Liquid Chromatograph equipped with a diode array detector. Detection was at 227 nm. The mobile phase of 1:1 $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (containing 0.5% H_3PO_4) was linearly increased to 85% CH_3CN over ten minutes. At a flow rate of 1.5 mL/min, the retention time of purified taxol (Investigational Drug Branch, NCI) was 5.2 minutes. Plasma samples from patients treated with taxol contained a peak with a retention time of 5.2 minutes, which was absent from blood samples drawn immediately before taxol administration. As evaluated by the diode array detector, this peak represented a single compound with a UV spectrum identical to that of taxol.

Taxol concentrations were calculated from HPLC runs using an HP3390A integrator by comparison with a standard curve. Standard curves of taxol were found to be linear over a concentration range of 0.7 $\mu\text{mol/L}$ to 100 $\mu\text{mol/L}$ taxol. The extraction efficiency of taxol from plasma was determined by spiking plasma samples from each patient with purified taxol to a final concentration of 2 $\mu\text{mol/L}$; these were analyzed with each patient's unspiked samples as described above. Extraction efficiency was 56% \pm 3.3% (mean \pm SEM, $n = 23$ samples).

Half-life values were calculated from log concentration v time curves using the method of residuals and a two-compartmental model.¹⁷ Other pharmacokinetic parameters were calculated using model-independent methods. The total area under the curve (AUC) was calculated using the linear trapezoidal method with extrapolation of the terminal phase to infinity. Total plasma clearance was calculated by dividing the dose by AUC, and the apparent volume of distribution at steady state and mean residence time (MRT) were calculated based on the area under the moment curve.¹⁸

The extent of plasma protein binding of taxol was assessed by equilibrium dialysis. Taxol, dissolved in cremophor vehicle, was added at various concentrations to human type AB serum (Sigma, St Louis). The spiked serum (1.4 mL) was then dialyzed (Spectrapor 3 membrane tubing) against phosphate buffered saline in a plexiglass dialysis cell for 18 hours at 25°C with constant mixing. Aliquots from each side of the cell were then simultaneously withdrawn, extracted as described above, and analyzed by HPLC to determine the concentrations of free, total, and (by subtraction) bound drug.

Table 2. Patient Characteristics (N = 26)

Male/female	11/15
Median age (range)	55 (21-83)
Median performance status (range)	1 (0-2)
Primary tumor type	
Melanoma	12
Renal cell	5
Adenocarcinoma of colon	3
Adenocarcinoma of lung	1
Ovarian	1
Squamous cell of nasopharynx	2
Neurofibrosarcoma	1
Adenocarcinoma of unknown primary	1
Prior treatment*	
None	2
Surgery only	7
Radiotherapy	8
Chemotherapy	13
1-2 Regimens	11
> 2 Regimens	2
Hormonal therapy	2
Immunotherapy	2

*Some patients are included in more than one category.

RESULTS

Sixty-five courses of taxol were administered to 26 patients enrolled in the study. Demographic characteristics of the patients are included in Table 2, and dosing information is given in Table 3.

Toxicity

Neurotoxicity was determined to be the dose-limiting toxicity. Neuropathic symptoms developed within 48 hours of treatment and typically included tingling and numbness of the hands and feet. Several patients also noted dysesthesias with prominent hyperpathia. Neurologic examination revealed distal sensory loss to large (vibration, proprioception) and small (pin prick, temperature) fiber modalities in most patients. All patients with symptoms of peripheral neuropathy developed significant decrease or loss of deep tendon reflexes. Although motor disturbances were usually mild or absent, two diabetic patients developed severe, generalized weakness, which transiently prevented ambulation. Both patients were treated at 250 mg/m² of taxol, and also developed a transient paralytic ileus, which may have been an additional manifestation of autonomic neuropathy. Neuropathic signs and symptoms steadily improved in those patients who had discontinued therapy. However, some patients continued to experience some

evidence of neuropathy for months. Because of the nature of a phase I study, it is not possible to be more precise about the reversibility of the neuropathy.

In two patients who initially had neuropathic symptoms following treatment with taxol, amitriptyline, 50 mg orally daily, was initiated and pain was substantially improved.

Bone marrow suppression primarily manifested as neutropenia was observed at all doses tested. There was no significant difference in grade of myelosuppression with increasing dosage. Nadir WBC counts occurred on day 10 (mean) with recovery on day 15 (mean). Platelet counts and hematocrit were not significantly affected by treatment.

One patient developed stridor during her second course of therapy after 4 mL of the infusion. Taxol was immediately discontinued, the patient was treated for presumed acute hypersensitivity reaction, and her symptoms were reversed. She was taken off study. There were no other hypersensitivity episodes among the 26 patients with a total of 65 courses of taxol administered (Table 4).

Pharmacology

The pharmacokinetics of taxol were examined in nine patients treated at three dose levels, 200, 250, and 275 mg/m². Taxol plasma concentrations increased during the 24-hour infusion period, and began to decline immediately upon cessation of drug infusion (Fig 1). The peak plasma concentrations were significantly correlated ($P < .05$) with dose, with a linear correlation coefficient of 0.72. Average peak plasma concentrations were 0.56, 0.88, and 0.94 $\mu\text{mol/L}$ at the three dose levels, respectively (Table 5).

Plasma disappearance curves appeared to be

Table 3. Dose Escalation Schedule

Dose (mg/m ²)	No. of Patients	No. of Courses
125*	1	3
150	5	9
190*	1	1
200	6	22
250	10	21
275	5	10

*Patient initially entered and treated at 250 mg/m², then at 190 mg/m². Dose reduced again by 25% because of peripheral neuropathy.

Table 4. Toxicity

Symptom	Dose (mg/m ²)*			
	150	200	250	275
Acute hypersensitivity reaction	0/5	0/6	1/10	0/5
Rash/pruritis/flushing	0/5	2/6	2/10	3/5
Neutropenia	5/5	6/6	9/9	5/5
	Gr 2 (1)			
	Gr 3 (1)		Gr 3 (1)	Gr 3 (1)
	Gr 4 (3)	Gr 4 (6)	Gr 4 (8)	Gr 4 (4)
WBC nadir $\times 10^3/\mu\text{L}$ median (range)	1.5 (0.8-3.4)	1.6 (0.8-4.7)	2.4 (0.7-3.4)	2.0 (1.1-2.3)
Peripheral neuropathy	0/5	3/6	4/10	4/5
		Gr 1 (3)	Gr 1 (1)	Gr 1 (1)
			Gr 2 (2)	Gr 2 (3)
			Gr 3 (1)	

Abbreviation: Gr, grade.

*Number in parentheses indicates number of patients.

multiphasic; the mean half-lives for the α and β phases ranged from 0.27 to 0.44 hours and 2.89 to 3.93 hours, respectively (Table 1). Total body clearance averaged 359 ± 26 mL/min/m² for all patients and was also not significantly correlated with dose. Differences in MRT among the three treatment groups were small, but MRT was significantly correlated with dose ($r = .92$). Complete urine collections were available from six patients, and in all instances $<5\%$ of the administered taxol was excreted unchanged.

Despite large patient-to-patient variability, a statistically significant ($P < .05$) correlation was found between dose and apparent volume of dis-

tribution (V_D) ($r = .73$). The calculated values obtained for V_D suggested that taxol was substantially bound to plasma proteins and other cellular components; in equilibrium dialysis studies, approximately 97.5% of the taxol was bound to human serum components over a wide range of drug concentrations (Fig 2).

Tumor Responses

Although measurable disease was not a requirement for entry into the study, tumor measurements were recorded before and after treatment whenever possible. Objective responses in patients with metastatic melanoma were initially observed at 200 mg/m², and subsequently a total of 12 patients with metastatic melanoma were treated as dosages were escalated. Treatment response could be evaluated in all 12 metastatic melanoma patients (Tables 6 through 8). Four of the patients had partial responses (33%) and two had minor responses to treatment. The partial responders had response durations of 13, 16, 16, and 22+ weeks.

DISCUSSION

Taxol was selected for clinical investigation because of its unique structure and mechanism of action, as well as its demonstrated anticancer effects in murine tumors and human tumor xenografts. When administered as a three-hour infusion in a phase I trial,¹⁰ hypersensitivity reactions were treatment-limiting. In another phase I trial,¹⁶ taxol was initially administered as a one-

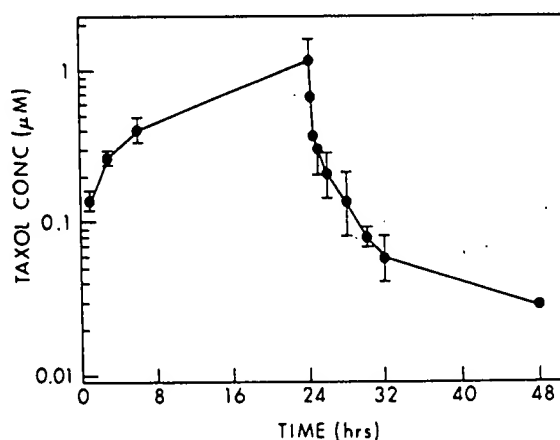


Fig 1. Plasma pharmacokinetics of taxol. Taxol was administered in a continuous IV infusion for 24 hours at a dose of 275 mg/m² (time 0 to 24). At specified intervals, plasma concentrations of taxol were determined, as described in Methods. Values are means \pm SEM for three patients.

Table 5. Pharmacokinetic Parameters of Taxol From Patients Treated With a 24-Hour Infusion at Three Dose Levels

Patient No.	Dose (mg/m ²)	Peak Plasma Concentration (μmol/L)	AUC (h mg/L)	Half-Life (h)		Cl* (mL/min/m ²)	V _D (L/m ²)	MRT (h)	Urine Excretion† (% dose)
				α	β				
1	200	0.54	9.27	0.62	2.28	350	33	13.9	5.0
2	200	0.51	8.04	0.55	ND	414	107	15.7	ND
3	200	0.64	11.90	0.14	3.49	280	54	15.2	1.7
Mean		0.56	9.74	0.44	2.89	348	65	14.9	3.4
4	250	0.97	15.00	0.45	2.55	278	93	17.6	1.7
5	250	0.77	9.90	0.27	3.56	421	146	18.4	1.8
6	250	0.90	13.30	0.20	2.85	313	92	16.9	0.83
Mean		0.88	12.70	0.31	2.99	337	110	17.6	1.4
7	275	1.27	17.20	0.29	3.77	267	104	18.5	ND
8	275	0.88	10.10	0.22	4.20	454	237	20.7	1.4
9	275	0.67	10.00	0.31	3.83	458	206	19.5	ND
Mean		0.94	12.40	0.27	3.93	393	182	19.6	1.4

Abbreviation: ND, not determined.

*Cl, apparent total body clearance.

†Infusion plus 24 hr postinfusion excretion of unchanged taxol.

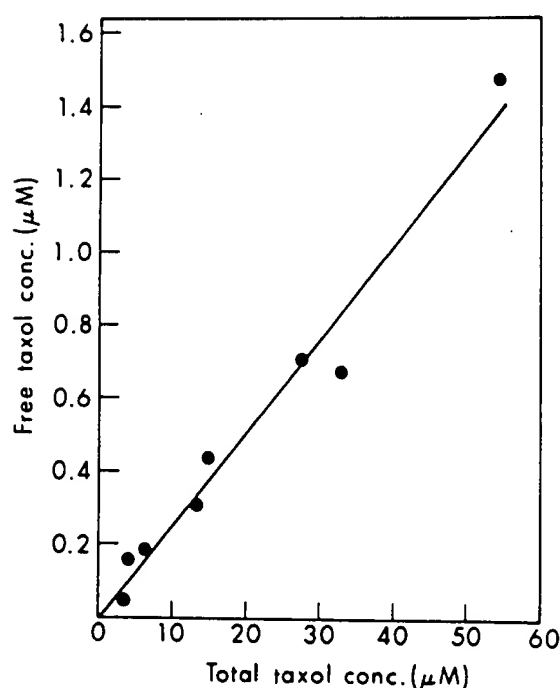


Fig 2. Serum protein binding of taxol. The extent of binding of taxol to human serum was determined by equilibrium dialysis (18 hours at 25° C) as described in Methods. A statistically significant correlation ($r = .96$) was found between the total and free concentrations of taxol over a range of 3 to 50 μmol/L taxol. Each point represents a single determination.

hour infusion and extended to six hours with a premedication regimen of dexamethasone, diphenhydramine, and cimetidine. During the shorter infusion and without premedication, acute hypersensitivity reactions were the most serious toxicities observed. With the extension of the infusion and with the premedication, no such reactions were observed. The dose-limiting toxicity in that trial was neuropathy and bone marrow suppression at 275 mg/m². Bone marrow suppression in that trial and in another phase I trial¹⁴ using a 24-hour infusion was not observed to be dose-related. This phase I study was conducted to define the dose-limiting toxicity of the drug administered as a 24-hour infusion which, in animal studies, was therapeutically superior to other schedules. This trial confirms that with premedication and extension of the infusion to 24 hours, acute hypersensitivity reaction is a rare event. Premedication as used in this study and close monitoring during initiation of the infusion are recommended in future trials.

Neutropenia was observed at all doses evaluated and was not dose-related. Neutropenia was significant, with grade 4 toxicity observed at all doses, but recovery was rapid. Two neutropenic deaths occurred in patients who had been dis-

Table 6. Clinical Responses to Taxol

Tumor	Dose (mg/m ²)	No. of Patients	Response
Melanoma	200	2	1 PR; 1 MR
	250	7	3 PR; 1 SD; 2 PD; 1 NE
	275	3	1 SD; 2 PD
Renal	200	3	2 SD; 1 PD
	275	1	1 SD
Colon	150	2	2 PD
	275	1	1 PD
Lung	150	1	1 PD
Ovarian	150	1	1 PD
Nasopharyngeal	250	1	1 PD
Neurofibrosarcoma	200	1	1 PD
Adenocarcinoma of unknown primary	250	1	1 PD

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease; MR, mixed response; NE, not evaluable (this patient died before he could be evaluated for response).

charged from the hospital. Although not documented in these uncooperative patients, death was probably due to sepsis. Thrombocytopenia was not observed.

The dose-limiting toxicity of taxol in this study was neuropathy. Neuropathy was initially observed at 200 mg/m² and increased in severity at 250 mg/m² and 275 mg/m². Neuropathy occurred at a lower dose than in our previous study of a shorter infusion time.¹⁶ This suggests that sustained drug exposure may be more neurotoxic than peak plasma concentration. Neuropathy occurred as early as after the first course of taxol in the present study.

Tissue culture studies provide a potential mechanism for the observed neurotoxicity. In organotypic dorsal root ganglion spinal cord cultures, taxol exposure leads to the formation of unusual numbers and arrays of microtubules in neurons, satellite cells and Schwann cells.¹⁹⁻²² In vivo, the dorsal root ganglion cells are particularly vulnerable to neurotoxins because of the special permeability of their blood vessels. Sensory symptoms may result from taxol-induced aggregation of microtubules in dorsal root ganglion cells. Motor symptoms may result from the involvement of anterior horn cells in a similar pathological process. In the tissue culture system, insulin antagonizes the action of taxol on the anterior horn cell. This may explain the greater vulnerability of a diabetic patient to motor neuropathy.

With the exception of hair loss, the other side

effects (fatigue, mild nausea, pruritis) associated with treatment were insignificant and easily tolerated.

Taxol was shown to have activity in metastatic melanoma in this study, with four of 12 patients achieving a partial response. An insufficient number of patients with other malignant diseases was entered to detect activity, if any.

The responses are presumed to result from taxol administration rather than cimetidine, although the latter agent has been reported to have activity against malignant melanoma.²³⁻²⁵ The reasons for this presumption are (1) only one 300-mg cimetidine dose was administered every 3 weeks to our patients, whereas patients said to respond to cimetidine with or without interferon received that dose four times daily for weeks,²⁶ (2) most patients who have been reported to respond to cimetidine and interferon received intratumoral injections of interferon,²⁷ and (3) studies in which the activity of cimetidine against melanoma could not be confirmed have begun to appear.²⁶⁻²⁹ Therefore, it is concluded that it is

Table 7. Melanoma Patients Treated With Taxol

Dose (mg/m ²)	No. of Patients Entered	No. of Courses*
200	2	10 (5,5)
250	7	14 (4,3,2,2,1,1,1)
275	3	7 (3,2,2)

*Numbers in parentheses indicate courses per patient.

Table 8. Clinical Responses in Melanoma Patients*

Dose (mg/m ²)	Prior therapy	Measurable disease	Response†	Duration (wk)
200	DTIC/RT	Lymph nodes	MR	12
200	Velban, Cytosan, CCNU/RT	Neck mass, liver, chest mass	PR (64%)	13
250‡	Part vulvectomy	Vulvar lesion, lymph nodes	PR (76%)	22 +
250	BCG	Satellite skin lesions	PR (80%)	16
250	Surgery	Skin lesions	ED (NE)	
250	Surgery/DTIC	Retroperitoneal mass	PD	
250	None	Neck mass, nodes	PR (72%)	16
250	None	Liver	SD	Off study due to toxicity
250	Surgery/RT	Liver, lung, skin, bone	PD	
275	Surgery	Skin	MR	4
275	Surgery	Lung	PD	
275	BCG, Dibromodulcitol, BMT, BCNU	Skin nodules, adenopathy	PD	

Abbreviations: CCNU, lomustine; DTIC, dacarbazine; RT, radiotherapy; BCG, bacillus Calmette-Guérin; BMT, autologous bone marrow transplant; BCNU, carmustine; PR, partial response; MR, minimal response; ED, early death; NE, not evaluable; PD, progressive disease; SD, stable disease.

*Twelve patients entered; 12 patients evaluable.

†Percent (%) is percentage of maximum tumor response.

‡Treated with one course at 250 mg/m², dose subsequently reduced to 190 mg/m², then 125 mg/m² due to toxicity, but with continued response.

unlikely that cimetidine influenced response rate, quality, or duration in this study.

The results of this trial suggest that taxol can be safely administered to patients with premedication to avoid acute hypersensitivity reactions. Although neuropathy is dose-limiting, there may

be a potential for ameliorating sensory symptoms with amitriptyline. Phase II trials with this schedule at a dose of 250 mg/m² are recommended. We have initiated phase II studies of taxol at that dose on this schedule in melanoma and in other solid tumors.

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